BONE SUBSTITUTE MATERIAL WITH A SURFACE COATING OF PEPTIDES HAVING AN RGD AMINO ACID SEQUENCE

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Abstract of **WO 9836782 (A2)**
Translate this text

The invention relates to a bone substitute material based on a porous polymer material the surface of which is coated with peptides having an RGD amino acid sequence.

Description – Machine Translation

Bone substitute with a surface allocation with peptides with RGD amino acid sequence the invention relates to bone substitute based on a porous polymer material, which exhibits a surface allocation with peptides with RGD amino acid sequence.

Bottom bone substitutes are materials to be understood, which serve as implants for the replacement or the reconstitution of bone structures due to defects after illness or operative engagements caused by an accident. Exemplarily to call implant molded articles are such as bone prostheses of most diverse type, bone liaison vehicles approximately in the form of Markraumnägein, bone screws and east EO synthesis plates, implant materials for the replenishment of Spongiosa bone

defects or of tooth-extraction-hollow as well as to the plastic surgical treatment of outline defects in the Kiefer Gesichtsbereich.

For the a healing process such become! it mplantatmaterialien as particularly favorable considered, which exhibit an high bioactivity, i.e. going by that they become in the organism believed and integrated in it. In case of of bone substitute this means that it is to grow together soon with body-own tissue, in particular with the bone, solid and durably.

It is known that so far the most favorable results of A HEALINg practical only with body-own materials, D. h. thus with bone transplants, achieved become. The availability of bone transplants is nature in accordance with limited. Autologe of grafts, thus grafts from the same individual are, if at all in suitable form and amount pre hands, only by at least an additional operative engagement more removable, whereby again an additional healing procedure to
Withdrawal place conditional becomes. Same one applies also in principle to homologous grafts thus grafts of donor individuals of the same type.

With these still problems of the compatibility in addition as well as today the not yet complete risk of infection which can be excluded come along

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Viruses, like in particular Hepatitis-und HIV viruses. Further the storage of donor material is in bone banks expensive and finally temporal only limited one.

Implant materials for the bone replacement from not body-used synthetic or from body-used materials can show, depending upon nature and nature an bioinert to bioactive behaviors.

The results of A HEALINg of body-own bone transplants could become so far however still by no synthetic implant material achieved.

Newer findings show that the knöchernen integration tmptantatmateriats first a cellular settlement of the surface must precede. Whereupon a deposition extracellular matrix follows and the formation again bone tissues. The entire procedure is multifactorial and becomes substantial affected of the properties of the bone substitute, the Vitalität of the knöchernen bearing and the biomechanical circumstances.

Known ones are the good to very good osteokonduktiven properties of calcium phosphate ceramics, Hydroxylapatit haltigem bone cement and particular polymers, itself in particular by one hydrophi! e surface distinguish. The good Osteokonduktivität of these materials does not tässt itself however frequent with optimized biomechanical
Properties combine, then particularly the ceramics brittle are and a little adaptable on the elastic requirements in the bone.

A possibility to stimulate the cellular adhesion on surfaces was found with the discovery of the integrins (proteins in the cell membrane). The integrins recognize amino acid sequences, for example the RGD sequence, on structural proteins and bind to it. Thus those becomes
Adhesion of cells in the body controlled.

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The feed of implant surfaces with synthetic accessible peptides with RGD sequences with the object to accelerate the a healing of the implants is known. With the known implants han it delt itself usually around metallic prostheses, in particular from titania and/or.

Titanium alloys. But here still no convincing implants with corresponding results are present, which could approach to the results of A HEALINg of body-own bone transplants.

The invention was the basis the problem definition to make a bone substitute available which cannot only cause the cellular adhesion, but the also rapid knöchern integrated will can, and thus a biological activity exhibits, which from body-own bone transplants the if possible close comes.

It was now found that this from a bone substitute achieved becomes, which is essentially constructed from a porous polymer material with a surface allocation with peptides with RGD amino acid sequence.

The feed of implant surfaces with synthetic accessible peptides with RGD sequences is known. With the known and tested implants it acts usually around metallic prostheses, in particular out of titania and/or. Titanium alloys. Further known (for example from the WHERE 91-05036) is, surfaces as from Poly meren, metals or also ceramic materials with peptides, those and. A. also
RGD sequences to exhibit can to treat. In this cases who these peptides however the targeted covalent bonded. The surfaces mentioned become corresponding with reactive groups activated and with coupling reagent with the peptides a reacted, whereby the peptides become covalent bonded. Are however no references contained, which to the porous polymere bone spare according to invention materials, which become loaded with peptides (thus no targeted ago guidance of covalent bonds), which the cell adhesion on the upper the flat implants stimulate, would lead.

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Subject-matter of the invention is therefore a bone substitute on base of a porous polymer material, which exhibits a surface allocation with peptides with RGD amino acid sequence.

Subject-matter of the invention is in particular a such bone substitute, which is present as implant molded article.

Subject-matter of the invention is also an implantation set from two or more separate components, whose a component an invention gemässes bone substitute and another component a liquid preparation of a Peptides with RGD amino acid sequence leg hold.

Furthermore subject-matter of the invention is the use of peptides with RGD amino acid sequence to the loading of the surface of a porous and/or surface-structured polymer material for the bone replacement, whereby a biological activation by stimulation of the cell adhesion on this surface made.

Further subject-matter of the invention is a method to the biological activation of bone substitutes on base of a porous Poly mermaterials by stimulation of the cell adhesion at their surface, which is characterized by the fact that one their surface with a liquid
Preparation of a Peptides with RGD amino acid sequence occupied.

Polymer materials represent an otherwise little biocompatible material, which in their mechanical properties at the bone adapted to become to be able, but so far not when bone replacement used become, because they do not connect themselves with the bone.

The relevance of the instant invention lies now in the fact that this little biocompatible polymer material, that from mechanical reasons

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as bone replacement desired would very probably be, by the loading with RGD peptides optimized and the biocompatibility achieved becomes.

Prefered ones are essentially thereby porous polymeric materials, those Polyacryl and/or polymethacrylates, polymethyl methacrylates (PMMA), polyethylenes (PE), Polypropylene (PP) and/or polytetrafluoroethylenes (ptfe) represent. Naturally also copolymers can become polymers mentioned among themselves as well as copolymers of this polymers with other polymers used. The preparation of such polymer materials i sp the skilled person well known and must become not more near explained here.

In a preferable embodiment the porous polymer material is present as Implantafformkörper in the bone substitute according to invention, or it forms the surface or a surface coating of an implant molded article in an other preferable embodiment.

In particular such shaped bodies according to invention are prefered, which point a partial or complete interkonnektierendes pore system up. Polymers with such pore systems kdinen for example prepared become the analogous way described in the patent application EP 0,705,609. The other one the skilled person however the general methods are not to the preparation of porous polymer mA probably terialien known and it must therefore other on it einge courses here become. Furthermore materials of this type are hältlich also in the commerce he. Their composition and the type of their processing are that
Skilled person common.

Prefered ones are thereby also polymers or composites from polymers and inorganic or metallic additions, in particular in particle or
Fiber form.

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If the polymer material is appropriate as poises implantant forwards, then it can become for example after the methods written in EP that already mentioned 0,705,609 by punctual fusion of Polymethyl methacrylat particles (PMMA) prepared. This method becomes essentially so performed that one nenten three various Kompo blended with one another. The first component is thereby a solid component, existing from a finely divided polymer of Acryl-und/or methacrylic acid esters (these polymers is in the commerce available) as well as if necessary other additions such as polymerization catalysts, Roentgen contrast means, fillers and dyes. The second component is a liquid component, existing from acryl and/or Methacrylsäureestermonomeren, if necessary with additions such as polymerization accelerators and stabilisers. The third Kompo nente consists of grobteiligen granulates, of a biocompatible material with largest particle diameter from 0,5 to 10 mm. Prefered materials are based on polyacrylates and/or polymethacrylates, polyolefins, copolymers of acrylates with styrene and/or butadiene as well as epoxy resins. The three main components become together brought and mixed with one another. After intimate mixing of the components the polymerization begins by the contained catalyst; for the period of some minutes the measures liquid to plastic remain more deformable, afterwards the cured final product is present. So thus porous implants can become from bone cement particles prepared, which preferably exhibit a interkonnektierende porosity. Dung in accordance with Erfin these materials become then with RGD contained
Peptides loaded. This porous bone substitute can in conventional manner during the liquid and/or. plastic stage as bone cement for the implantation of bone prostheses used become.

The surgeon can convert also the mass to shaped bodies of arbitrary form and Gröl3e and these after the cure to the reconstruction of
Bone defects or as local active substance depots into those which can be treated
Body regions implantieren.

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In a preferable embodiment the porous polymere materials points a middle mesh size from 0.05 mm to 2.50 mm, separates prefered 0.10 mm up to 1.25 mm up.

According to invention thus the surface of the implant molded article must exhibit a porous form, what for example in the form realized can be that a composite or a bone cement is provided with a porous surface coating or a corresponding roughened surface.

If the porous polymer material forms the surface or the surface coating of an implant molded article, then these can consist of all known and conventional implant materials, if them with a layer from porous polymer coated to become to be able. Implan of doing materials can become into the classes inorganic, in particular ceramic materials, physiological acceptable metallic materials, physio logical acceptable polymeric materials and composites from two or more materials of the mentioned type divided.

As inorganic materials for example materials come into question, which are based on calcium haltigen materials, like in particular calcium carbonate, calcium phosphates and from these compounds of derived systems. From the group of the calcium phosphates are as prefered hydroxyapatites to call tricalcium phosphate and Tetracalciumphosphat.

Implant materials on inorganic base ensure however usually an high mechanical stability only if them as ceramics, D. h. thus in the form of with sufficient high temperatures sintered materials and/or. Workpieces used become.

Details to bone ceramic(s) and particularly favorable methods to their preparation can for example the patent documents

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DE 37 27 606, DE 39 03 695, DE 41 00 897 and DE 40 28 683 removed become.

As metallic material major titanium or a titanium becomes alloy used. Particularly interesting is also group materials, which take a substantial broader range off in their mechanical properties than pure polymers. So also the combination of such materials with other implant Kompone is beside the application with RGD peptides coated polymers as bone replacement. of great importance.

As example for such a combination the composite of a metal is prosthesis (z. B. To call titanium) with treated a according to invention porous polymer. In addition z becomes. B. the titanium implant on actual knew manner for the composite with the polymer treated. This can happen for example after the Kevioc method or the Sulicoater method (described in DE 42 25 106). A layer from porous polymer becomes then for example analogous on the pretreated titanium surface applied, in the EP 0,705,609 described manner. The polymere-coated part of the prosthesis becomes then subsequent coated with the RGD peptide.

An other preferable embodiment of this invention represents the subsequent implant material. In place of the titanium implant a corresponding implant becomes from a GRP components material (carbon fiber and epoxy resin) with a porous layer from z. B. PMMA coated, subsequent takes place the Peptid coating. Such an implant has to create the advantage of the bone-adapted elasticity, a boundary layer-free bone Implantat Interface and to achieve an optimum force application from the implant in the bones. Clinical one becomes thereby a bone resorption by " stress squinting thing " avoided and the prosthesis keeps more prolonged.

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The porous polymeric layer, which becomes on a corresponding implant material applied, has preferably a layer thickness of
0.2 mm up to 25 mm, in particular prefered from 2.0 mm to 20 mm.

The middle mesh size preferably lies within the range of 0.05 mm to
2.50 mm, prefered in particular is the range from 0.10 mm to
1.25 mm.

As insertable according to invention peptides with RGD sequence all come
Peptides and their compounds with nichtpeptidischen substituent, which the amino acid sequence arginin glycine aspartic acid (RGD) to contain and which can adhärieren over their peptidischen and nichtpeptidischen substituents on the polymer surfaces, in considerations.

The subsequent enumerating of prefered peptides and/or. Peptide compounds are only exemplary ones and no limiting Character have, whereby the subsequent abbreviations become used: Asp = aspartic acid Gly = glycine
Badly = arginine
Tyr = tyrosine
Ser = serine
Phe = phenylalanine
RGD (bad Gly Asp), GRGD (Gly bad Gly Asp), GRGDY (Gly bad Gly Asp Tyr), RGDS (bad Gly Asp Ser), GRGDS (Gly bad Gly Asp Ser), RGDF (bad Gly Asp Phe), GRGDF (Gly bad Gly Asp Phe), compounds of
Peptides with fatty acids or also acrylate-substituted RGD peptides. Those
Peptides can be both linear and cyclic.

The coating of the bone substitutes according to invention with one
Peptide compound or a peptide with RGD sequence is actual

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problem-free. One appropriately proceeds from a suitable ftüssigen solution of the corresponding peptide, becomes immersed into which the material which can be loaded. With the fact shown could become that the END valid occupancy of the implant surface is in a wide range relative independent of the concentration of the solution. With very much low concentrations tionszeit exactly the same a complete loading of the surface can become achieved by corresponding extension of the Exposi.

As prefered concentration range for the Peptidlösung 10 ng 100 ug/ml indicated can become. The exposition time amounts to preferably 10 minutes to 24 hours.

The surface allocation with peptides, amounts to preferably 50% to 100% of the free surface.

The Peptidsubstanz adhäriert thereby without other treatment solid on the polymeric surface. The implants become on conventional manner steri more lisier, for example by y-irradiation, heat or ethylene oxide, and are then implantation.

In a preferable embodiment the bone substitute according to invention in form of a ready for use implantation set from two or more separate components is present, where a component a porous polymer material, preferably as implant molded articles, and another component a liquid preparation of a Peptides also
RGD sequence included. A such embodiment is particularly convenient, in order to meet possible stability problems, which could arise with a long-term storage from already finished ready-made bone according to invention substitutes, effective. On idiom of the bone substitutes according to invention in form of a such implantation set made in the manner that one short forwards or during the surgical engagement for the implantation the porous

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polymere implantation material with the RGD peptidecontained solution in the prescribed manner loads.

Depending upon embodiment stelit thus the bone according to invention substitute a at least equivalent replacement for homologous and autologe bone transplants or is healing-restrained for other forms of the bone replacement a significant improvement regarding in.

The bone substitutes according to invention do not only cause a cellular adhesion by the immobilization of peptides with RGD sequence on a porous polymer implant, but it could become in experiments detected that these implant materials significant integrate themselves more rapid knöchern as untreated implants.

The positive influence of the RGD coating on the a healing behavior of implants for the bone replacement is more portable, like already mentioned, on practical all types of bone substitutes and implant materials over, if these so constituted and/or. designed are that they consist either completely or partly of porous polymer material, or that the implants with such a porous polymeric layer coated are.

Also for example implants, which exhibit a porous structured or at least roughened surface, fulfill this prerequisite.

Grundsätziich can be present the bone substitutes according to invention not only as implant molded articles, but also in powder,
Granulates, Partiel or fiber form, depending on how it requires the place of work and the application purpose.

Also without other embodiment is assumed
Skilled person the above description in furthest scope to use can. The preferable embodiments are therefore only as

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descriptive to understand by no means as disclosure limited in any manner.

The complete disclosure of all vor-und appended listed applications, patents and publications are introduced by reference into this application.

The subsequent examples are representative for the instant invention.

Example 1 A) preparation of a porous polymere shaped body
A low viscous bone cement (composition: 31 g polymethyl methacrylate/Polymethylacrylt (94/6) - copolymer, 6 g Hydroxyl apatite powder, 3 g zirconia) is touched with 30 ml methyl methacrylat monomer on conventional manner. The Kompon ducks contains the starter system Dibenzoylperoxid/Dimethyl p toluidin. This dough 100 g become pure, cylindrical polymethyl metacrylate granulates (diameter 2 mm, length 3 mm thorough with the bone cement dough) added and mixed.

The mixed mass in polypropylene forms given and one <ässt approx. 15 min. harden. It results intekonnektierend a porous body with a porosity of 20%. b) Loading of the polymere shaped body with RGD peptide
After A) obtained shaped bodies becomes by immersion into one
Solution of the Tetrapeptides GRGD concentration 100 ug/ml,
Exposition time approx. 60 minutes, with this RGD peptide loaded and final dried. Subsequent one became in a cell adhesion test the success of the coating measured. The results

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it shows that the empty cylinders practical are not settled by cells, while the inventive materials into the depth of the pores show inside a dense cell lawn.

Example 2 experimental studies animal species: Rabbit of implants: a) porous RPM mA shaped body b) PMMA shaped body according to invention with GRGD coated
Both implants became by y-irradiation sterilized and implanted in Kaninchenfemora.

Implantation place: Into the Patellagleitlager of the Femora, left-sided and rechtsseitig.

After 2 weeks the Knocheneubildung and the Mineralisation become detected by histoiogische study.

Result: a) PMMA
The implant camp shows only a thin circular ring neuge bildeter Knochentrabekel, which is penetrated with connective tissue. A direct support of the Knochentrabekel on the cement beads is not more discernible.

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b) PMMA + GRGD
Here a solid trabekuläre bone new formation can become found, which encloses three-quarter the entire implant; the Knochentrabekel is more immediate supported the cement beads.

Claims 1. Bone substitute on base of a porous polymer material, characterised in that it an upper flat allocation also Peptides with RGD amino acid sequence exhibits.

2. Bone substitute according to claim 1, characterised in that the porous polymer material as Implantafformkörper is present.

3. Bone substitute according to claim 1 or 2, characterised in that the porous polymer material the surface or a surface coating of an implant molded article forms.

4. Bone substitute after one of the claims 1 to 3, characterised in that the porous polymer material the surface or a surface coating of an implant molded article forms, which consists of an inorganic or a metallic material or of a composite.

5. Bone substitute after one of the claims 1 to 4, characterised in that the porous polymer material essentially Polyacryl and/or polymethacrylate, polymethyl methacrylate, polyethylene, polypropylene and/or polytetrafluoroethylene and/or a copolymer from these polymers with other polymers is.

6. Bone substitute after one of the claims 1 to 5, characterised in that these porous shaped bodies a partial or complete interkonnktierendes pore system exhibit.

7. Bone substitute after one of the claims 1 to 6, characterised in that the surface allocation with peptides also RGD amino acid sequence 50% to 100% of the free surface amounts to.

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8. Implantation set from two or more separate components, its a component a bone substitute after one of the claims 1 to 7 and another component a liquid Präpa ration of a Peptides with RGD amino acid sequence included.

9. Use of peptides with RGD amino acid sequence to charge of the Oberftäche of a porous and/or oberftächenstruk polymer material for the bone replacement, whereby a biological activation by stimulation of the cell adhesion on these Oberf) äche turierten erfotgt.

10. Method to the biological activation of bone spare materials on base of a porous polymer material through Stimulation of the cell adhesion at their surface, characterised in that one their upper pool with a liquid Preparation of a Peptides with RGD amino acid sequence occupied